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EXAMINER	
GREENE, IVAN A	

ART UNIT	PAPER NUMBER
1619	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/567,345	BESSE, JEROME	
	Examiner	Art Unit	
	IVAN GREENE	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26 and 28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

Claims 1-26 and 28-31 are currently pending. Claim 27 has been canceled by applicant. Claims 1-26 and 28-31 are presented for examination on the merits.

The instant office action is being made Non-Final because new references have been made of record that more expressly teach the composition limitation of claim 12 and the method steps of claims 28-31.

All rejections and/or objections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments.

Priority

The U.S. effective filing date has been determined to be 08/05/2004, the filing date of the document PCT/FR04/50376. The foreign priority date has been determined to be 08/06/2003, the filing date of document FRANCE 0350403.

Rejections

Claim Rejections - 35 U.S.C. 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 29, 30 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

2. Claim 29 is rejected as being indefinite because the claim recites --granulation of a mixture of metformin appropriate amounts-- in item (a) (5). It is unclear what "metformin appropriate amounts" means because the claim also recites --from 65% to 90% by weight of metformin active ingredient-- in item (a) (1).

3. Claim 29 is further rejected as being indefinite because the claim recites the limitation "the mixture of excipients forming (ii)" in item (c). There is insufficient antecedent basis for this limitation in the claim.

4. Claim 30 is rejected as being indefinite because the claim recites --granulation of a mixture of metformin appropriate amounts-- in item (a) (5). It is unclear what "metformin appropriate amounts" means because the claim also recites --from 65% to 90% by weight of metformin active ingredient-- in item (a) (1).

5. Claim 30 is further rejected as being indefinite because the claim recites the limitation "the mixture of excipients forming (ii)" in item (c). There is insufficient antecedent basis for this limitation in the claim.

6. Claim 31 is rejected as being indefinite because the claim recites --granulation of a mixture of metformin appropriate amounts-- in item (a) (5). It is unclear what "metformin appropriate amounts" means because the claim also recites --from 65% to 90% by weight of metformin active ingredient-- in item (a) (1).

7. Claim 31 is further rejected as being indefinite because the claim recites the limitation "the mixture of excipients forming (ii)" in item (c). There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1-11, 13-16 and 18-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over TIMMINS (US 6,031,004) and BALKAN (US 2003/0139434) as evidenced by TYLER (W.S. TYLER CANADA, product and price catalog), MARTIN (US 6,110,497) and SHIMIZU (US 6,328,994).

Applicants Claims

Applicant claims a dispersible or orodispersible solid pharmaceutical composition having the form of particles with a size lower than 710 µm, containing a metformin active ingredient, wherein the particles comprise: (a) from 65% to 90% by weight of the metformin active ingredient, optionally provided in the form of a salt, or a combination of the metformin active ingredient with a hypoglycemic active ingredient; (b) from 0.5 to 4% by weight of a binding agent or a combination of binding agents; (c) from 1% to 12%

by weight of a disintegrating agent or a combination of disintegrating agents; (d) from 0% to 10% by weight of a diluting agent or a combination of diluting agents; (e) from 0.05% to 3% by weight of a sweetening agent or a combination of sweetening agents; and (f) one or more additional excipients, the weight percentages being expressed based on the total weight of said composition.

Determination of the scope

and content of the prior art (MPEP 2141.01)

TIMMINS teaches novel salts of the anti-diabetic agent metformin including metformin fumarate and metformin succinate which may be employed alone or in combination with another anti-hyperglycemic agent (abstract). TIMMINS further teaches the dosage form can be formulated as a tablet or capsule, among others (4:49-52). TIMMINS further teaches the dosage form(s) of their invention may included from about 1% to about 80% of excipients such as lactose, sugar, corn starch, modified corn starch, mannitol, sorbitol, calcium carbonate, and microcrystalline cellulose (5:8-12). TIMMINS further teaches the formulations my comprise one or more binders such as polyvinylpyrrolidone (having a molecular weight of preferably about 40,000), lactose, starches and polyethylene, among others (5:15-23). TIMMINS further teaches disintegrants, such as croscarmellose sodium, crospovidone [cross-linked polyvinylpyrrolidone], sodium starch glycolate, corn starch and microcrystalline cellulose, are included in a preferred amount of about 2% to about 8% by weight (5:24-30). TIMMINS further teaches other excipients such as preservatives, silicon dioxide

and polymeric celluloses (5:34-46). TIMMINS further teaches in examples 9 and 10 the sweetening agent xylitol, and the flavoring agents grape flavor, spice flavor and raspberry flavor (10: 1-35).

TIMMINS teaches the example four (7:29-60) with the following ingredients:

Ingredient	Amount per tablet (mg)
Metformin (2:1) succinate	600.0 mg
Microcrystalline cellulose NF	80.0 mg
Croscarmellose sodium NF	45.0 mg
Hydroxypropylmethyl cellulose (5 cps) (HPMC) USP	15.0 mg
Magnesium Stearate NF	8.0 mg

wherein the active agent metformin succinate is present in an amount of 80% (600/748*100), the binder hydroxypropylmethyl cellulose is present in an amount of 2% (15/748*100), the disintegrant croscarmellose sodium is present in an amount of 6% (45/748*100), the filler/diluting agent microcrystalline cellulose is present in an amount of 10% (80/748*100), and includes the additional excipient magnesium stearate. TIMMINS further teaches the formulation (of example 4) is prepared by wet granulation and includes the steps of mixing, granulating, drying and compressing into tablets (7:45-60).

TIMMINS teaches the additional active ingredients including pioglitazone (3:64), thiazolidinedione [also called glitazone] (4:2), glimepride, glipyride, glipizide, chlorpropamide, gliclazide and acarbose (4:24-26), among others.

Regarding the size of the granules, TIMMINS teaches the mixtures are passed through a #12 to #40 mesh screen (6:3), which according to TYLER indicates a size of 425 microns to 1.7 mm (see TYLER: p. 3, table cols. 1 & 2).

Ascertainment of the difference between

the prior art and the claims (MPEP 2141.02)

The difference between the rejected claims and the teachings of TIMMINS is that TIMMINS does not expressly teach a dipeptidyl peptidase inhibitor; the sugar coating; or the core being 75% to 85% of tablet weight. The deficiencies in the dipeptidyl peptidase inhibitor and the sugar coating are cured by the teachings of BALKAN.

BALKAN teaches combination pharmaceutical compositions which include dipeptidyl peptidase four (DPP-IV) inhibitors and at least one anti-diabetic compound (abstract). BALKAN further teaches the preferred embodiment in which the anti-diabetic compound is selected from metformin, among others ([0150]). BALKAN further teaches the example comprising DPP728 plus metformin ([0175]). BALKAN further teaches the pharmaceutical preparations according to the invention are prepared in a manner known [in the art], for example conventional mixing, granulating, sugar-coating ([0190]). BALKAN further teaches if desired granulating a mixture, and processing the mixture or granules to give tablets or sugar-coated tablet cores ([0190]).

It would have been obvious to adjust the core to 75% to 85% of the tablet weight. For example SHIMIZU (US 6,328,994) teaches orally disintegrable tablets comprising a coating layer wherein (15:20-40):

> The ratio of the "coating layer" to the "core" can be selected within the range in which it is possible to control dissolution of the physiologically active substance and particle size of the composition, for example, usually about 50 to 400 weight % relative to 100 weight % of the core.

Where the disclosed ratio of "coating layer" to the "core" {(50%:100%) 0.5:1 to (400%:100%) 4:1} overlaps with the range clamed by applicant {(75%:25%) 3:1 to (85%:15%) 5.67:1}. And MARTIN (US 6,110,497) teaches a dispersible tablet formulation composed of granulate particles and extragranular excipients wherein (col. 2):

> In the tablet formulation the granulate may suitably comprise 70% or more, e.g. 80% or more, 90% or more or 95% or more of the total tablet weight so that a high proportion of medicament is present.

Therefore it would have been obvious to adjust the core to 75% to 85% of the tablet weight.

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine a DPP-IV inhibitor with a metformin pharmaceutical composition, as suggested by BALKAN, and produce the instantly claimed invention because TIMMINS suggest the use of metformin in combination with another anti-diabetic drug and BALKAN teaches DPP-IV inhibitors as anti-diabetic drugs suitable for use with metformin. One of ordinary skill in the art would have been

motivated to combine BALKAN with TIMMINS because formulation produced would have had an increased efficacy by the combination of two anti-diabetic drugs. It would have been obvious to produce a sweetener-coated formulation because the sweetener would have a more appealing taste for the user and increased patient compliance.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

Response to Arguments:

Applicant's arguments filed 11/02/2009 have been fully considered but they are not persuasive.

Applicant's argument that TIMMINS fails to disclose or suggest the preparation of dispersible or orodispersible dosage forms, is not convincing because the preamble statement "a dispersible or orodispersible solid pharmaceutical formulation" has been regarded as intended use and so long as the prior art structure is capable of performing the intended use as recited in the preamble then it meets the claim (see MPEP § 2111.02 - (II)).

Applicant's argument that, although the active ingredient is sieved in TIMMINS, the steps of adding additional excipients to the sieved active ingredient, followed by mixing and compressing [...] will result in a mixture containing particles that are larger than 710 µm, is acknowledged. In response the examiner argues that *the process is not contrary to the process of the instantly claimed invention*. TIMMINS teaches the formulation (of example 4) is prepared by wet granulation and includes the steps of mixing, granulating, drying and compressing into tablets (7:45-60). Furthermore, it is clear from the instant specification that the broadest reasonable interpretation of --A dispersible or orodispersible solid pharmaceutical composition having the form of particles with a size lower than 710 µm-- includes tablets composed of particles with sizes lower than 710 µm:

> in an aqueous solution. More specifically, the pharmaceutical composition which has been developed allows for metformin based tablets to be produced which disintegrate after an immersion time in water lower than 3 minutes, as measured according to the standard from European Pharmacopeia (4th edition). This immediate disintegration effect is obtained more particularly by virtue of using, for producing the tablets of the invention, granules of the pharmaceutical composition with a size lower than 710 µm.

([0018], as published). And it is noted that Webster's defines "particle" as "any of the basic units of matter and energy (as a molecule, atom, proton, electro or photon)." Therefore the limitation, as currently recited, reads on the atoms and molecules composing the dosage form.

2. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over TIMMINS (US 6,031,004) and BALKAN (US 2003/0139434) as evidenced by TYLER (W.S. TYLER CANADA, product and price catalog) as applied to claims 1-11, 13-16 and 18-28 above, and further in view of BONHOMME (US 6,372,790).

Applicants Claims

Applicant's claims are discussed above. Applicant further claims the dispersible or orodispersible solid pharmaceutical composition further comprises a fibrate-type hypocholesterol agent.

Determination of the scope

and content of the prior art (MPEP 2141.01)

The teachings of TIMMINS and BALKAN are discussed above and incorporated herein by reference.

TIMMINS and BALKAN do not expressly teach the combination of metformin with a fibrate-type hypocholesterol agent.

BONHOMME teaches a pharmaceutical composition comprising (i) metformin and (ii) a fibrate selected from fenofibrate and bezafibrate for use in the treatment of non-insulin-dependent diabetes (abstract). BONHOMME further teaches

> The combination of a hypoglycaemic agent and of an anti-lipaemic agent has already been envisaged in the art, and especially for treating diabetics also displaying hyper-lipaemia.

(1:42-45), and further teaches:

> insulin-dependent diabetes. More specifically, a synergistic effect has been obtained by combined administration of metformin and of a fibrate chosen from fenofibrate and bezafibrate. The same advantageous results have been observed using a pharmaceutically acceptable salt of metformin in combination with one of these two fibrates.

(2:3-8).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine a metformin active agent with a fibrate-type hypochlosterol agent, as suggested by BONHOMME, and produce the instantly claimed invention because the combination would have resulted in a synergistic effect. One of ordinary skill in the art would have been motivated to combine a metformin active agent with a fibrate-type hypochlosterol agent because the formulation produced would have had an increased efficacy by acting synergistically. Furthermore, a person having ordinary skill in the pharmaceutical art because the combination has been successfully used in the prior art, for example in the invention of BONHOMME, in combination formulations.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

3. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over TIMMINS (US 6,031,004) and BALKAN (US 2003/0139434) as evidenced by TYLER (W.S. TYLER CANADA, product and price catalog) as applied to claims 1-11, 13-16

and 18-28 above, and further in view of OHNO (US 4,017,598); and further evidenced by BENNET ("Pharmaceutical Production: An engineering guide," 2003, Institution of Chemical Engineers, Chapter 6, pp. 111-153).

Applicants Claims

Applicant claims a method for preparing a hydrodispersible non film-coated pharmaceutical tablet comprising the steps of (a) preparing (i) an internal core comprising an dispersible or orodispersible solid pharmaceutical composition having the form of particles with a size lower than 710 μm, containing a metformin active ingredient, the composition as described above, through wet granulation of a mixture of metformin; (b) drying the granule obtained in step (a); and (c) adding to the granules obtained in step (b) and a sweetening agent; and (d) performing a compression of the granules.

Determination of the scope

and content of the prior art (MPEP 2141.01)

TIMMINS teaches novel salts of the anti-diabetic agent metformin including metformin fumarate and metformin succinate which may be employed alone or in combination with another anti-hyperglycemic agent, as discussed above (abstract). TIMMINS further teaches the formulation (of example 4) is prepared by wet granulation and includes the steps of mixing, granulating, drying and compressing into tablets with the additional extragranular excipients (microcrystalline cellulose and magnesium stearate) (7:45-60).

BALKAN teaches combination pharmaceutical compositions which include dipeptidyl peptidase four (DPP-IV) inhibitors and at least one anti-diabetic compound, as discussed above (abstract). BALKAN further teaches the preparation process including the steps of mixing ingredients in a high shear mixer and granulating using water, drying the wet granules and passing them through a screen, then mixing with extragranular excipients (croscarmellose sodium, silicon dioxide and magnesium stearate) in a V-blender, and finally compressing into tablets ([0208]).

Ascertainment of the difference between

the prior art and the claims (MPEP 2141.02)

The difference between the rejected claim and the teachings of TIMMINS/BALKAN is that TIMMINS/BALKAN do not expressly teach the addition of a sweetener as an extragranular excipient before the final step of tablet compression. This deficiency in the addition of a sweetener as an extragranular excipient before the final step of tablet compression is cured by the teachings of OHNE. BENNET is relied upon as teaching the knowledge of a person having ordinary skill in art of pharmaceutical formulation at the time the claimed invention was made.

OHNO teaches the preparation of readily disintegrating tablets, a method useful for tableting some medicinals of poor tabletability (title, abstract). OHNO further teaches the method according to their invention includes forming granules of methylcellulose and a medicinally active ingredient and admixing with a disintegrator and optionally sweetening agents such as sucrose, fructose (3:5-11; 28-33; 44-50; 60-68).

Resolving the level of ordinary skill in the pertinent art

A person having ordinary skill in the art at the time the claimed invention was made would have recognized the claimed method steps are no more than conventional steps for producing tablets as evidenced by BENNET. BENNET teaches the process of tablet making using modern machinery involves the blending of drug substance with binders, fillers, coloring materilas, lubricants, etc., followed by a series of steps to increase the bulk density and uniformity of the mixture and prevent segregation of the drug (p. 112 § 6.1.4, lines 1-4). BENNET further teaches the process of wet granulation in figure 6.2 which clearly includes the conventional steps of wet granulation, drying, mixing with a lubricant, etc., and compression into tablets as follows (p. 115):

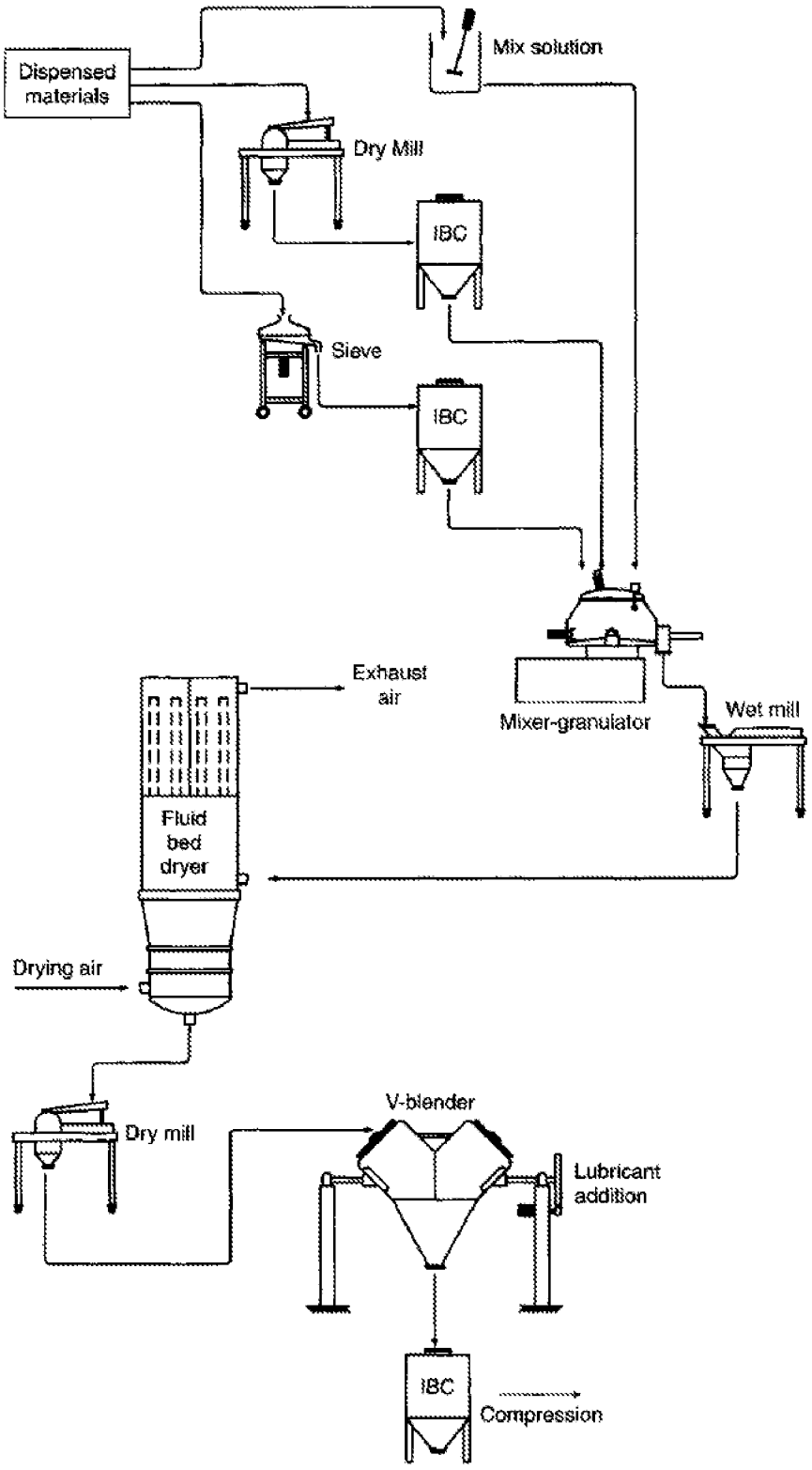

Figure 6.2 Typical wet granulation process

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for preparing a pharmaceutical formulation including the conventional steps of wet granulation, drying, mixing the obtained granulate with excipients such as sweeteners and compressing into tablets, instantly claimed invention because the wet granulation process would have produced a dosage forming having a uniform distribution of ingredients and allowed for the easy handling of the drug product during the tableting process. One of ordinary skill in the art would have been motivated produce a method for preparing a pharmaceutical formulation including the conventional steps of wet granulation, drying, mixing the obtained granulate with excipients such as sweeteners and compressing into tablets because the wet granulation process is well established, the equipment and process parameters widely available. Furthermore the wet granulation process provides the advantage of lower dust formation as discussed by BENNET (p. 113, lines 6-7).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

4. Claims 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over TIMMINS (US 6,031,004) and BALKAN (US 2003/0139434) as evidenced by TYLER (W.S. TYLER CANADA, product and price catalog) as applied to claims 1-11, 13-16 and 18-28 above, and further in view of VENKATESH (US 6,475,510); and further evidenced by BENNET ("Pharmaceutical Production: An engineering guide," 2003, Institution of Chemical Engineers, Chapter 6, pp. 111-153).

Applicants Claims

Applicant further claims a method for preparing a hydrodispersible non film-coated pharmaceutical tablet comprising the steps of (a) preparing (i) an internal core comprising a dispersible or orodispersible solid pharmaceutical composition having the form of particles with a size lower than 710 µm, containing a metformin active ingredient, the composition as described above, through dry granulation of a mixture of metformin; (b) compacting the dry granules obtained in step (a); and (c) adding to the granules obtained in step (b) and a sweetening agent; and (d) performing a compression of the granules.

Applicant further claims a method for preparing a hydrodispersible non film-coated pharmaceutical tablet comprising the steps of (a) preparing (i) an internal core comprising a dispersible or orodispersible solid pharmaceutical composition having the

form of particles with a size lower than 710 μm, containing a metformin active ingredient, the composition as described above, through dry granulation of a mixture of metformin; (b) adding to the granules obtained in step (b) and a sweetening agent; and (c) performing a compression of the granules.

Determination of the scope

and content of the prior art (MPEP 2141.01)

TIMMINS teaches novel salts of the anti-diabetic agent metformin including metformin fumarate and metformin succinate which may be employed alone or in combination with another anti-hyperglycemic agent, as discussed above (abstract). TIMMINS further teaches the formulation (of example 4) is prepared by wet granulation and includes the steps of mixing, granulating, drying and compressing into tablets with the additional extragranular excipients (microcrystalline cellulose and magnesium stearate) (7:45-60).

BALKAN teaches combination pharmaceutical compositions which include dipeptidyl peptidase four (DPP-IV) inhibitors and at least one anti-diabetic compound, as discussed above (abstract). BALKAN further teaches the preparation process including the steps of mixing ingredients in a high shear mixer and granulating using water, drying the wet granules and passing them through a screen, then mixing with extragranular excipients (croscarmellose sodium, silicon dioxide and magnesium stearate) in a V-blender, and finally compressing into tablets ([0208]).

Ascertainment of the difference between

the prior art and the claims (MPEP 2141.02)

The difference between the rejected claims and the teachings of TIMMINS/BALKAN is that TIMMINS/BALKAN do not expressly teach the dry granulation or the addition of a sweetener as an extragranular excipient before the final step of tablet compression. This deficiency in the step of dry granulation and the addition of a sweetener as an extragranular excipient before the final step of tablet compression is cured by the teachings of VENKATESH. BENNET is relied upon as teaching the knowledge of a person having ordinary skill in art of pharmaceutical formulation at the time the claimed invention was made.

VENKATESH teaches a method for the manufacture of bite-dispersion tablets which disperse easily and quickly in the oral cavity, after a gentle bite, without the aid of water and, and if necessary includes masking the bitter taste of medicaments (abstract). VENKATESH teaches the problems overcome by their invention include (col. 3):

> A need exists for a cost effective, rapid operation process for producing tablets containing medicaments, which provide for ease of oral administration (fast disintegration in the mouth without water) and taste-masking of any bitter ingredients.

VENKATESH further teaches the manufacturing method includes the steps of (i) admixing at least one pharmaceutically active ingredient with one or more excipients; (ii) preparing the admixture of step (i) for compression by dry granulation (such as via slugging or roller compacting), milling and sieving; and (iii) blending the product of step (ii) with additional pharmaceutically acceptable excipients which comprise xylitol,

mannitol, maltodextrin or sorbitol; and optionally includes a flavoring agent, a sweetner/taste-masking agent, and a disintegrant; and (iv) compressing the mixture of step (iii) into tablets (3:39-57).

Resolving the level of ordinary skill in the pertinent art

A person having ordinary skill in the art at the time the claimed invention was made would have recognized the claimed method steps are no more than conventional steps for producing tablets as evidenced by BENNET. BENNET teaches the process of tablet making using modern machinery involves the blending of drug substance with binders, fillers, coloring materials, lubricants, etc., followed by a series of steps to increase the bulk density and uniformity of the mixture and prevent segregation of the drug (p. 112 § 6.1.4, lines 1-4). BENNET further teaches the process of dry granulation in figure 6.1 which clearly includes the conventional steps of blending the dry ingredients, compacting the dry granules, milling the granule, mixing with a lubricant, etc., and compression into tablets as follows (p. 115):

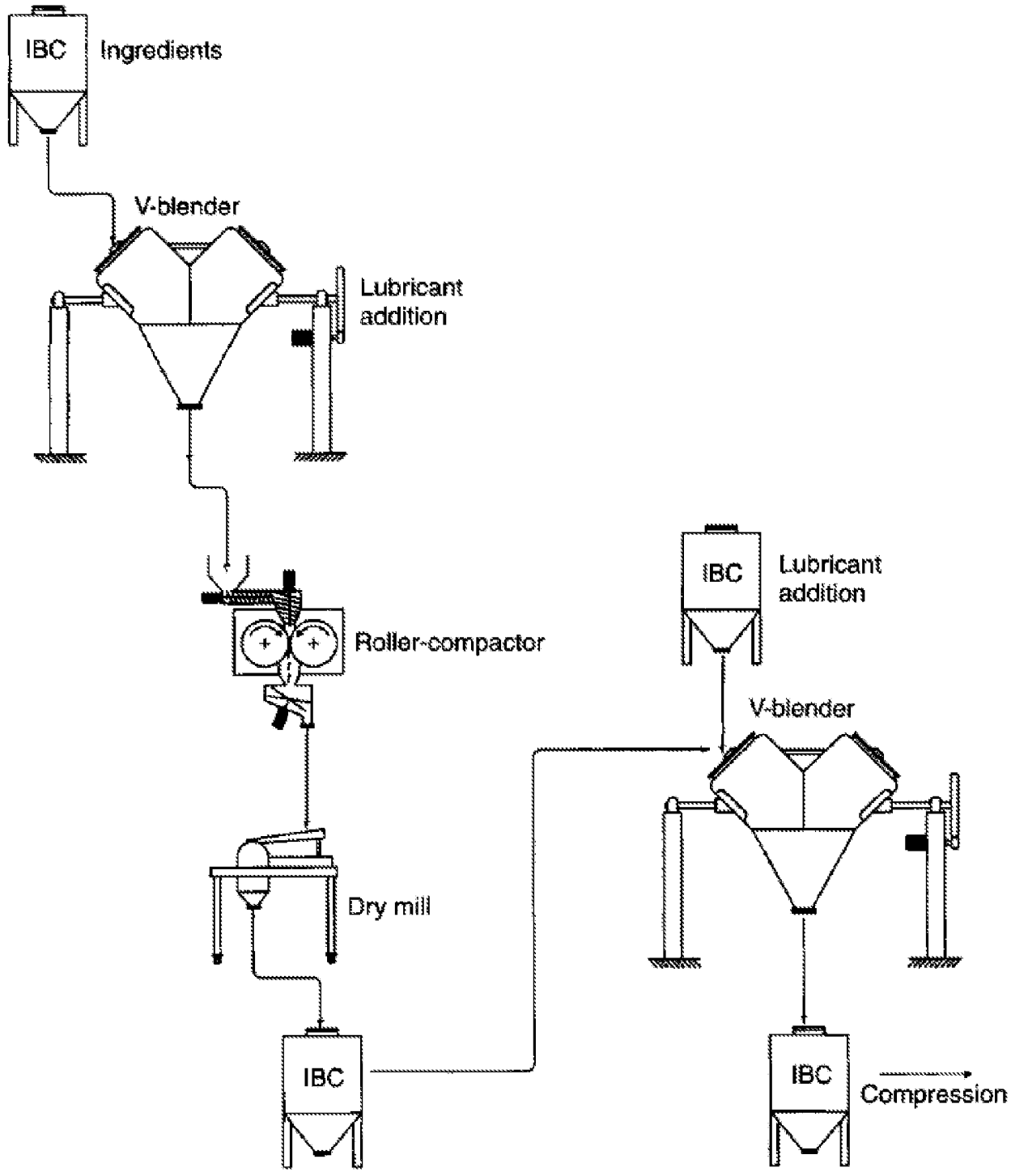

Figure 6.1 Typical dry granulation process

BENNET further teaches the advantages of dry granulation include lower capital equipment costs and a simpler process (p. 114, lines 1-4).

Finding of prima facie obviousness

Rationale and Motivation (MPEP 2142-2143)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to produce a method for preparing a pharmaceutical formulation including the conventional steps of blending the dry ingredients, compacting the granules, mixing the obtained granulate with excipients such as sweeteners and compressing into tablets**,** instantly claimed invention because the dry granulation process of dry granulation would have required a lower capital expenditure for equipment. One of ordinary skill in the art would have been motivated produce a method for preparing a pharmaceutical formulation including the conventional dry granulation process because the dry granulation process would have been more cost effective and rapid operation process for the production of tablets.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The following U.S. Patent documents are cited for applicant's consideration: MARTIN (US 6,110, 497); SHAH (US 5,370,878); PAN (US 5,130,333); DAUM (US 3,420,931); DAGGY (US 2003/0215505); SERPELLONI (US 2003/0147947); JAIN (US 6,316,029); SAUERBERG (US 6,274,608); and PATEL (US 2003/0180352). The following non-patent literature document is cited for applicant's consideration: KLEINEBUDDE (European Journal of Pharmaceutics and Biopharmaceutics, vol. 58, pp. 317-326).

Claims 1-26 and 28-31 are pending and have been presented for examination on the merits. Claims 29, 30 and 31 are rejected under 35 U.S.C. 112, second paragraph; and claims 1-26 and 28-31 are rejected under 35 U.S.C. 103(a). No claims allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to IVAN GREENE whose telephone number is (571)270-5868. The examiner can normally be reached on Monday through Thursday 7AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bonnie Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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